identical in both the entomological and the toxicological work with compound VII being somewhat superior to compound VI in both series of tests.

The authors are indebted to Dr. Frank B. Maughan of the Rohm and Haas Co., Philadelphia, Pa., and Dr. Ray Treichler, of the Fish and Wildlife Service, U. S. Department of Interior, for having rendered their skillful services in performing the entomological and toxicological work, respectively.

Summary

The preparation of four new compounds containing the arsenic-sulfur linkage has been described. These compounds were prepared by the action of mercaptans containing one or more sulfhydryl groups on chloroarsines.

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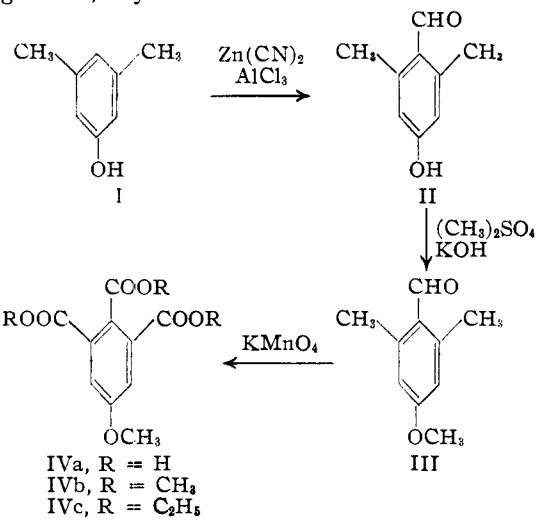
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Preparation of 5-Methoxybenzene-1,2,3-tricarboxylic Acid[1]

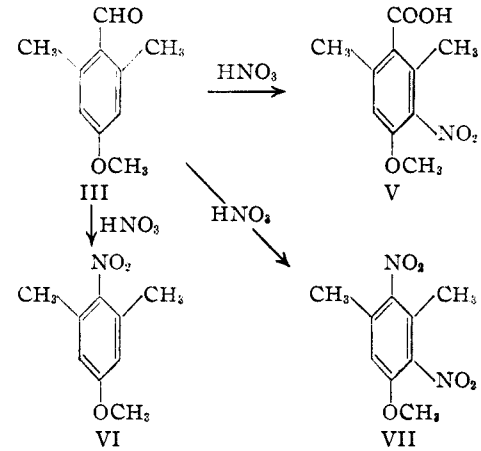
BY A. L. WILDS AND CARL DJERASSI[2,3]

A sample of 5-methoxybenzene-1,2,3-tricarboxylic acid (IVa) was wanted in connection with another problem.[4] We have synthesized this new acid according to the following scheme, starting with 3,5-xylenol



The acid was obtained in 52% yield as the trimethyl ester by alkaline permanganate oxidation of the methyl ether III, followed by methylation with diazomethane. The free acid and crystalline triethyl ester also were prepared.

Oxidation of the methyl ether III with nitric acid also was investigated. While this reagent did not prove suitable for preparing IVa, the results were of interest. When III was heated with concentrated nitric acid for fifteen minutes at reflux, 25% of the nitro acid V was isolated. In addition about 8% of the product VI in which the aldehyde group was replaced by a nitro group, and about 9% of the dinitro compound VII were



obtained. When the period of heating was increased to two hours, the yield of the nitro acid V was lowered to 15% and that of the dinitrodimethylanisole VII was raised to 30%. A similar susceptibility of the carboxyl group to cleavage in nitric acid solution has been observed by Jackson and Earle[5] in the nitration of anisic acid and by Reverdin[6] with *p*-dimethylaminobenzoic acid.

Experimental[7]

2,6-Dimethyl-4-hydroxybenzaldehyde (II) and 2,4-Dimethyl-6-hydroxybenzaldehyde.—The general procedure of Adams and Montgomery,[8] for the modified Gattermann reaction was followed, using 12.3 g. of 3,5-xylenol, 50 cc. of dry, thiophene-free benzene, 23.5 g. of zinc cyanide and 20 g. of aluminum chloride. After hydrolysis and steam distillation, 3.1 g. (20%) of 2,4-dimethyl-6-hydroxybenzaldehyde was isolated from the distillate, m. p. 47–48° (reported 48–49°),[9] and 9.45 g. (63%) of the other isomer, m. p. 186–190° with previous sintering, from the residue. Recrystallization from alcohol yielded 6.15 g. of long prisms of 2,6-dimethyl-4-hydroxybenzaldehyde (II), m. p. 195–196.5°, and 1.19 g. of m. p. 188–192° (reported,[9a,10] m. p. 190°).

(1) From part of the Ph. D. Thesis of Carl Djerassi.

(2) Wisconsin Alumni Research Foundation Research Assistant, 1943–1945.

(3) Present address, Ciba Pharmaceutical Products, Inc., Summit N. J.

(4) Wilds and Djerassi, THIS JOURNAL, **68**, 1712 (1946).

(5) Jackson and Earle, *Am. Chem. J.*, **29**, 104 (1903).

(6) Reverdin, *Ber.*, **40**, 2442 (1907).

(7) All melting points are corrected.

(8) Adams and Montgomery, THIS JOURNAL, **46**, 1518 (1924).

(9) (a) v. Auwers and Borsche, *Ber.*, **48**, 1713 (1915); (b) v. Auwers and Saurwein, *ibid.*, **55**, 2379 (1922).

(10) Gattermann, *Ann.*, **357**, 328 (1907).

The oxime of II, prepared by the sodium acetate-alcohol method, crystallized from petroleum ether–acetone as thin, prismatic needles, m. p. 202–202.5° (dec.). Gattermann[10] reported the m. p. 196°.

Anal. Calcd. for $C_9H_{11}O_2N$: C, 65.4; H, 6.7. Found: C, 65.7; H, 6.6.

The pyridine–alcohol method was unsatisfactory, giving unidentified material, m. p. 234–236° (found: C, 58.0; H, 6.3) as well as the impure oxime, m. p. 194–196° (dec.).

2,6-Dimethyl-4-methoxybenzaldehyde (III). A solution of 2 g. of 2,6-dimethyl-4-hydroxybenzaldehyde (II) in 20 cc. of 10% potassium hydroxide was warmed to 35° and treated with a total of 10 cc. of dimethyl sulfate and 3 cc. of 45% potassium hydroxide, added in three portions over 30 minutes. The product, which was isolated by ether extraction, crystallized upon trituration with petroleum ether (b. p. 40–60°) giving 1.82 g. (83%) of colorless solid, m. p. 45.5–47°. Distillation of a sample (b. p. 139–142° at 12 mm.) and recrystallization from petroleum ether gave stout prisms of m. p. 49.5–51°; v. Auwers and Borsche[9a] reported the m. p. 45–47°; Gattermann[11] reported the m. p. 18° for material obtained by the hydrogen cyanide synthesis from the methyl ether of 3,5-xylenol, but this undoubtedly was a mixture of isomers.

Trimethyl Ester (IVb) of 5-Methoxybenzene-1,2,3-tricarboxylic Acid (5-Methoxyhemimellitic Acid).—To a stirred suspension of 1.39 g. of the methyl ether III in 105 cc. of boiling 5% potassium hydroxide was added dropwise over a period of three hours a solution of 7.26 g. of potassium permanganate in 170 cc. of water. After one hour an additional 1 g. of permanganate was added in 40 cc. of water and the solution stirred at 90–100°. After seventeen hours an additional 0.8 g. of permanganate in 60 cc. of water was added; since the color persisted for two hours, the oxidation was stopped at this point by adding a small amount of methanol. The mixture was filtered and the manganese dioxide washed thoroughly with warm 5% potassium hydroxide. The filtrate was concentrated to about 75 cc., acidified to congo red with concentrated hydrochloric acid and allowed to evaporate. To remove the last traces of water and hydrochloric acid, methanol was added to the sirup, evaporated and the process repeated several times (this treatment resulted in partial methylation of the acid).

The dry salt mixture was digested with boiling methanol, filtered and the filtrate evaporated. The residue was methylated with ethereal diazomethane (from 3 g. of nitrosomethylurea) allowing to stand for twenty hours. Then the ether was evaporated and the methylation repeated. After four hours, the solution was evaporated to dryness, the residue dissolved in hot acetone and filtered. Following evaporation of the solvent, the material was crystallized from petroleum ether, giving 1.25 g. (52% yield) of the crude trimethyl ester, m. p. 74–79°. One recrystallization from petroleum ether-acetone gave material (75% recovery) as colorless blades, m. p. 82–83°. The analytical sample had the m. p. 83–83.5°.

Anal. Calcd. for $C_{13}H_{14}O_7$: C, 55.3; H, 5.0. Found: C, 55.5; H, 5.0.

When ethyl alcohol was substituted for methanol in removing the last of the water from the crude acid, and the material methylated as above, colorless prisms melting at 98–99° were obtained. Analysis indicated this product to be a dimethyl ethyl ester of the acid, resulting from partial esterification during the evaporation process.

Anal. Calcd. for $C_{14}H_{16}O_7$: C, 56.8; H, 5.4. Found: C, 56.5, 56.7; H, 5.3, 5.3.

5-Methoxybenzene-1,2,3-tricarboxylic Acid (5-Methoxyhemimellitic Acid IVa).—A solution of 600 mg. of the trimethyl ester in 10 cc. of methanol and 3 cc. of 45% potassium hydroxide was heated for four and one-half hours and then concentrated to a small volume, water added and again concentrated. Upon acidification with hydrochloric acid to congo red (total volume 35 cc. at this point), a colorless crystalline precipitate separated; weight 550 mg., m. p. 188–226° (gas). Several recrystallizations from a small amount of water gave thin, colorless needles, which softened at 185° and melted at 211–235° (dec.) This was apparently the dihydrate of the monopotassium salt of IVa. The anhydrous salt, obtained by drying at 80° (0.1 mm.) for two days, softened at 232° and melted at 235–237° with slight evolution of gas. An alkaline residue was left when a sample was burned.

The free acid was obtained by heating 200 mg. of the monopotassium salt with 8 cc. of concentrated hydrochloric acid and adding just enough water (about 10 cc.) to dissolve the solid in the boiling acid. Upon cooling 128 mg. of thin needles of the tricarboxylic acid were obtained which softened at 209° and melted at 211–212° with vigorous gas evolution. The m. p. was not changed by recrystallization from water. When the colorless melt was cooled it solidified and remelted at 191.5–192.5°. This may indicate the formation of an anhydride. The acid is soluble in methanol and hot water, slightly soluble in cold water and insoluble in ether.

Anal. Calcd. for $C_{10}H_8O_7$: C, 50.0; H, 3.4. Found: C, 49.7; H, 3.5.

The triethyl ester (IVc) was prepared by refluxing 72 mg. of the monopotassium salt for twenty hours with 35 cc. of absolute alcohol saturated with hydrogen chloride. After evaporation the residue was dissolved in ether, washed with bicarbonate solution, water, dried and evaporated. The ester was crystallized from petroleum ether (b. p. 60–68°) to give 38 mg., m. p. 63–67°. Further recrystallization gave colorless rhombs with the m. p. 69–70°.

Anal. Calcd. for $C_{16}H_{20}O_7$: C, 59.2; H, 6.2. Found: C, 59.1; H, 6.1.

Nitric Acid Oxidations of 2,6-Dimethyl-4-methoxybenzaldehyde (III). (a) Heating for Fifteen Minutes.—A mixture of 500 mg. of the methyl ether III and 2 cc. of concentrated nitric acid (sp. g. 1.42) was heated in an oil bath at 80°. After one minute a very vigorous evolution of oxides of nitrogen occurred. After the reaction subsided the solution was heated to reflux for fifteen minutes, cooled and diluted with water. The crystals which separated were filtered on a sintered glass funnel, washed thoroughly with water and dried; the mixture weighed 500 mg., m. p. 146–161°. The solid was dissolved in ether, washed well with 5% bicarbonate solution, water and the ether evaporated. Crystallization of the residue from ethanol gave 62 mg. (9%) of material of m. p. 160–164°. Further recrystallization from ethanol gave colorless, thin rods, m. p. 174–175°, of **3,5-dimethyl-2,4-dinitroanisole (VII)**; reported[12] m. p. 172°.

Anal. Calcd. for $C_9H_{10}O_5N_2$: C, 47.8; H, 4.5. Found: C, 48.1; H, 4.5.

The ethanol filtrate from above was evaporated to dryness and the residue (86 mg.) dissolved in hot petroleum ether (b. p. 60–68°), filtered, concentrated and triturated with low boiling (40–60°) petroleum ether; 20 mg. of material, m. p. 47–123° was removed. From the filtrate was obtained 45 mg. (8%) of yellow crystals, m. p. 46–48°. After two recrystallizations from dilute ethanol the melting point of the pale yellow needles was 48–50°. This material was **3,5-dimethyl-4-nitroanisole (VI)**. A mixture with the sample prepared below (m. p. 50–52°) melted at 49.5–51°. A mixture of the compound with the isomeric 3,5-dimethyl-2-nitroanisole (see below) or with the starting 2,6-dimethyl-4-methoxybenzaldehyde turned to an oil at room temperature.

The sodium bicarbonate washings (see above) were acidified, and the product extracted with ether. Recrystallization of the material from petroleum ether–acetone gave 171 mg. (25%) of colorless crystals of **2,6-dimethyl-3-nitroanisic acid (V)**, m. p. 188.5–189°. The analytical sample crystallized from the same solvent mixture as clusters of small needles, m. p. 189.5–190°.

(11) Ref. 10, p. 362.

(12) Rowe, Bannister, Seth and Storey, *J. Soc. Chem. Ind.*, **49**, 473T (1930).

Anal. Calcd. for $C_{10}H_{11}O_5N$: C, 53.3; H, 4.9. Found: C, 53.5; H, 4.9.

(b) **More Vigorous Oxidations.**—Using the same quantities as in (a), the solution was refluxed for twenty minutes, an additional 2 cc. of nitric acid was added and refluxing continued for one and one-half hours. After cooling in ice, the solution was filtered (without dilution) through sintered glass and the solid washed with concentrated nitric acid. No crystalline material was isolated from the filtrate. The colorless solid (376 mg., m. p. 151–163°) was recrystallized from ethanol to give 203 mg. (30%) of 3,5-dimethyl-2,4-dinitroanisole as colorless rods, m. p. 170.5–172°. Evaporation of the filtrate and recrystallization of the residue from petroleum ether–acetone gave 103 mg. (15%) of colorless needles of 2,6-dimethyl-3-nitroanisic acid, m. p. 189.5–190°.

Oxidation of the methyl ether (400 mg.) with 3 cc. of concentrated nitric acid and 8 cc. of water at 190° for twenty-four hours in a sealed tube gave a clear solution from which no crystalline material could be isolated. With one-half this amount of nitric acid and water, considerable carbonaceous material was formed.

Preparation of 3,5-Dimethyl-4-(and 2)-nitroanisole.—3,5-Xylenol was mono-nitrated and the two isomers were separated according to the procedure of Adams and Stewart.[13]

The nitrophenols were methylated by an adaptation of the procedure of Rowe, *et al.*,[12] which was satisfactory on a small scale. 3,5-Dimethyl-4-nitroanisole was obtained as thin nearly colorless needles from dilute alcohol, m. p. 50–52° (reported[12] 53°). 3,5-Dimethyl-2-nitroanisole, however, was obtained as a low melting crystallographic modification from dilute methanol as nearly colorless prismatic needles melting at 35–35.5°. Steam distillation of the material and recrystallization from methanol gave the known form melting at 43–44°.[12,13] When a melt of the lower form was seeded with the higher it solidified and remelted at 43–44°.

Summary

5-Methoxybenzene-1,2,3-tricarboxylic acid was prepared by permanganate oxidation of 2,6-dimethyl-4-methoxybenzaldehyde. The products resulting from treatment of this intermediate with nitric acid also were investigated.

(13) Adams and Stewart, THIS JOURNAL, **63**, 2861 (1941).

MADISON 6, WISCONSIN RECEIVED JANUARY 26, 1946

NOTES

Preparation of a Filaricide. *p*-[bis-(Carboxymethylmercapto)-arsino]-benzamide[1]

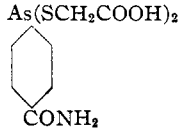
BY THOMAS H. MAREN

The screening of a large number of metal-organic and organic compounds against the filarial parasites, *Dirofilaria immitis* and *Litomosoides carinii*, of the dog and the cotton rat, respectively, revealed that phenyl arsenoxides as a class were outstandingly lethal to these organisms. Of twenty representative arsenoxides generously supplied by Dr. Harry Eagle,[2] the most favorable chemotherapeutic index was shown by *p*-arsenosobenzamide (I). Because of its low solubility in water, this compound was unsuitable for intravenous administration, and it became necessary to synthesize a compound which would retain the therapeutic activity of the parent and yet be adequately soluble for injection.

The condensation of *p*-arsenosobenzamide (I) and thioglycolic acid yields a thioarsenite, *p*-[bis-(carboxymethylmercapto)-arsino]-benzamide (II) whose disodium salt has the desired characteristics. This reaction was previously investigated by Gough and King.[3] In an attempt to make a particularly pure product on a larger scale, their method has been modified in several respects. The high As value found for their product suggests that 1–2% of unreacted *p*-arsenosobenzamide (I) may have been present. Introduction of a filtration step before crystallization of the final product (II) has eliminated the possibility of this type of contamination. Further changes in the proportions and manipulative procedure were made to prevent formation by hydrolysis of *p*-arsenosobenzoic acid (III) or its thioarsenite (IV). Since there is no nitrogen in III and IV, the nitrogen assay of the final product is a critical indication of the presence of these compounds. Since they are particularly toxic,[4] it is important to prevent their formation. Gough and King[3] did not report nitrogen values but it has been found that low nitrogen in the final product (indicating the presence of III or IV) is associated with overheating or recrystallization from aqueous solutions. In the present procedure these have been avoided, and both nitrogen and arsenic conform closely to the theoretical value for II.

Since properties of the thioarsenite (II) and its disodium salt have not been described previously, some of these are given below together with the revised method of synthesis.

II



Preparation of *p*-[Bis-(carboxymethylmercapto)-arsino]-benzamide (II).—In a typical experiment 11.45 g. (0.05 mole) of *p*-arsenosobenzamide (I) was suspended in 150

(1) This work was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and The Johns Hopkins University.

(2) Venereal Disease Research and Postgraduate Training Center, U. S. Public Health Service, Johns Hopkins Hospital, Baltimore, Maryland.

(3) Gough and King, *J. Chem. Soc.*, 669 (1930).

(4) Eagle, Hogan, Doak and Steinman, *Public Health Reports*, **59**, 765 (1944).